学位の種類	博士（医学）
報告番号	甲第１６１２号
学位記番号	第１１４７号
氏名	川口　洋平
授与年月日	平成 30 年 3 月 26 日
学位論文の題名	The janus kinase inhibitor tofacitinib inhibits TNFα-induced gliostatin expression in rheumatoid fibroblast-like synoviocytes （関節リウマチ線維芽細胞様滑膜細胞において，ヤヌスキナーゼ阻害剤であるトファシチニブは TNFα に誘導されるグリオスタチンを抑制する） Clinical and Experimental Rheumatology（in press）
論文審査担当者	主査：　和田 郁雄 副査：　岡本 尚，大塚 隆信

ABSTRACT

Objective: Gliostatin (GLS) is known to have angiogenic and arthritogenic activity, and GLS expression levels in serum from patients with rheumatoid arthritis (RA) are significantly correlated with the activity of the disease. Therefore, suppressing GLS activity may also be effective approach to treating RA. Tofacitinib is a novel oral janus kinase (JAK) inhibitor and is effective in treating RA. However, the mechanism of action of tofacitinib in fibroblast-like synoviocytes (FLSs) has not been elucidated. The purpose of this study was to investigate the modulatory effects of tofacitinib on serum GLS levels in patients with RA and GLS production in FLSs derived from patients with RA.

Methods: Six patients with RA who had failed therapy with at least one TNF inhibitor and were receiving tofacitinib therapy were included in the study. Serum samples were collected to measure CRP, MMP-3 and GLS expression. FLSs derived from patients with RA were cultured and stimulated by TNFα with or without tofacitinib. GLS expression levels were determined using reverse transcription-polymerase chain reaction (RT-PCR), EIA and immunocytochemistry, and signal transducer and activator of transcription (STAT) protein phosphorylation levels were determined by western blotting.

Results: Treatment with tofacitinib decreased serum GLS levels in all patients. GLS mRNA and protein expression levels were significantly increased by treatment with TNFα alone, and these increases were suppressed by treatment with tofacitinib, which also inhibited TNFα-induced STAT1 phosphorylation.

Conclusions: JAK/STAT activation plays a pivotal role in TNFα-mediated GLS up-regulation in RA. Suppression of GLS expression in FLSs has been suggested to be one of the mechanisms through which tofacitinib exerts its anti-inflammatory effects